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Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

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Citation (APA):
Larsen, J. B., Clergeaud Veiga, G., Eliassen, R., Melander, F., Kirchhausen, T., & Andresen, T. L. (2016). *Contructive delivery of cancer chemotherapeutics using virus inspired liposomes..* Poster session presented at 14th European Symposium on Controlled Drug Delivery, Egmond aan Zee, Netherlands.

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Constructive Delivery of Cancer Chemotherapeutics Using Virus Inspired Liposomes

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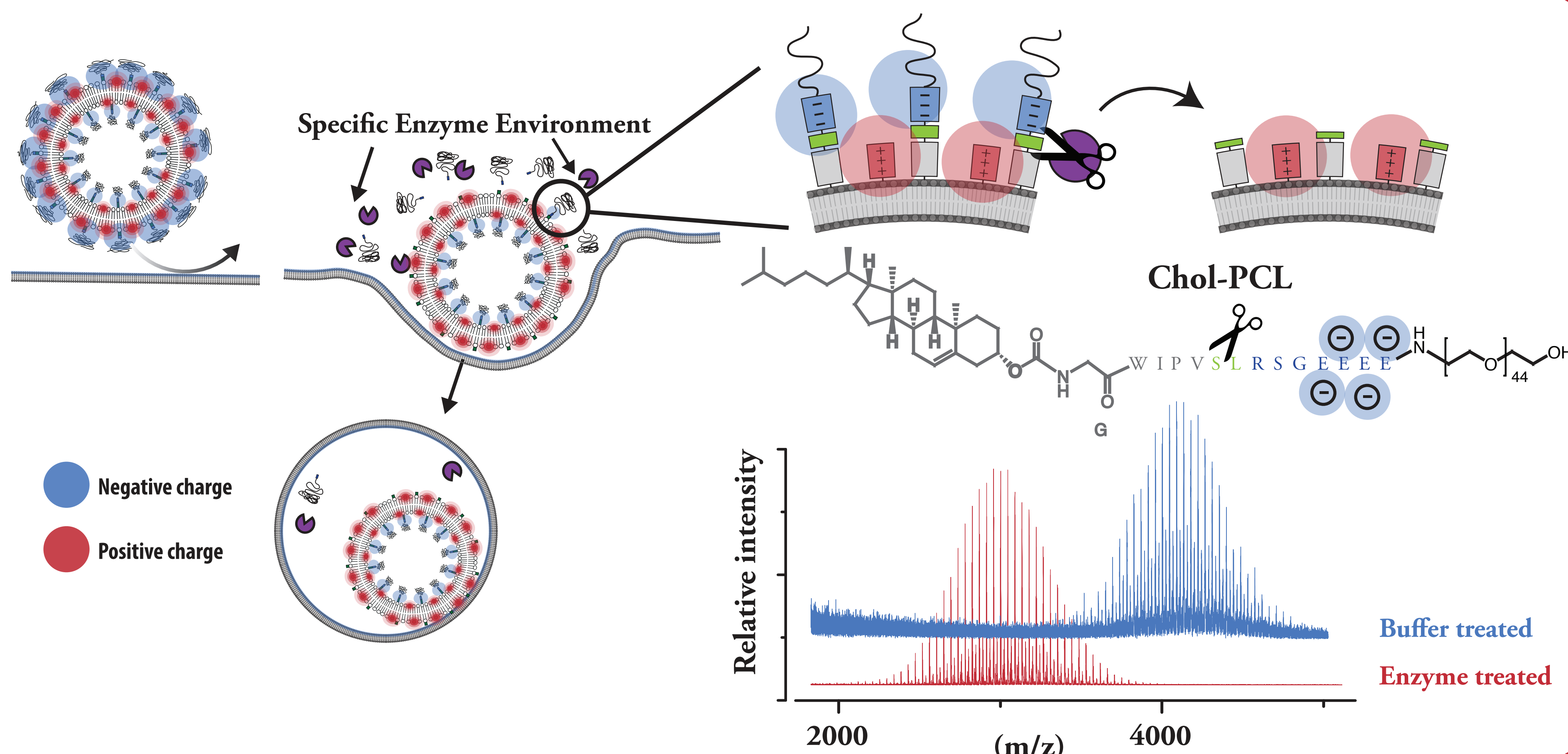
Concept

The liposome contains a PEGylated cleavable lipopeptide (PCL) which makes it responsive to matrix metalloprotease (MMP).

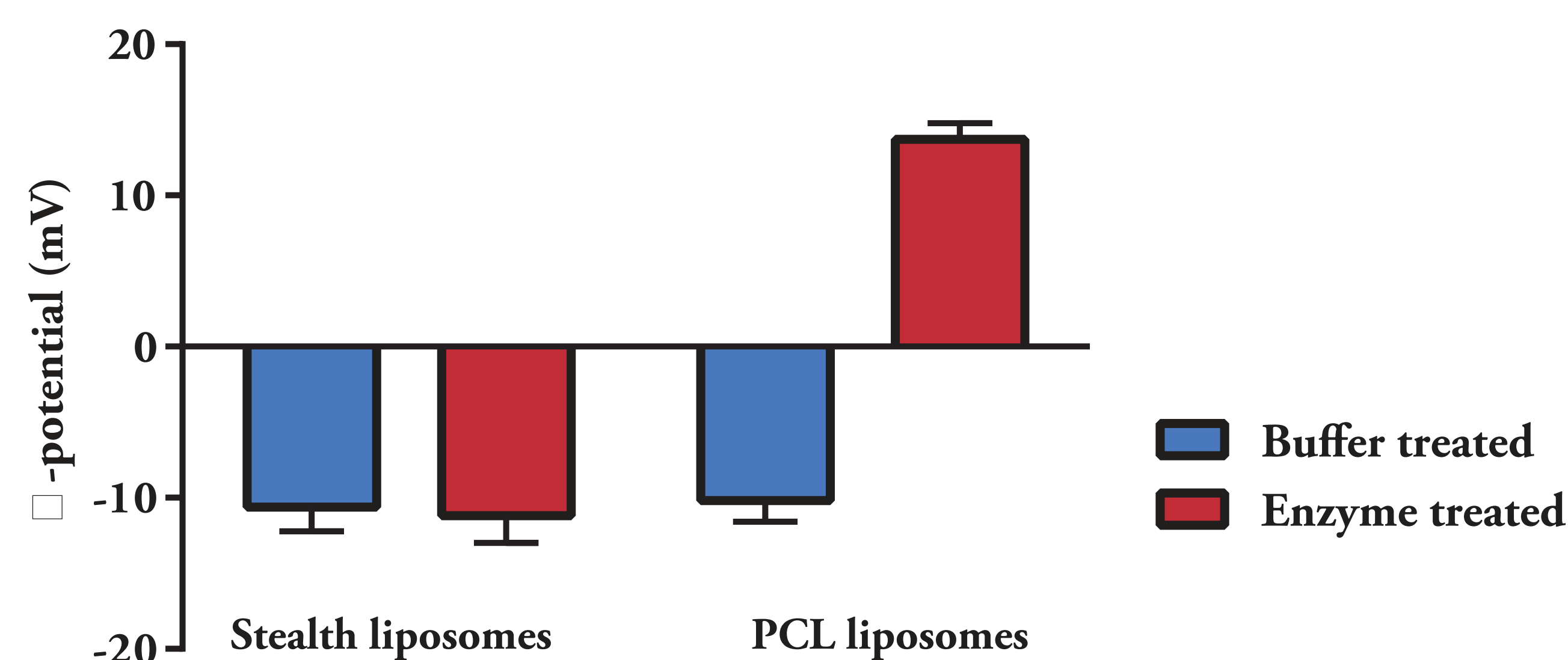
The PCL sequence contains four glutamic acid residues which provide the negative charge.

High MMP activity triggers the cleavage of PCL and thereby exposure of a concealed positive charge in the form of three arginine residues (R3) anchored by cholesterol. The exposure of R3 increases cell interaction and drug delivery.

In the future we hope to create a charge mediated fusiogenic liposome system, inspired by the very efficient delivery mechanism employed by viruses.

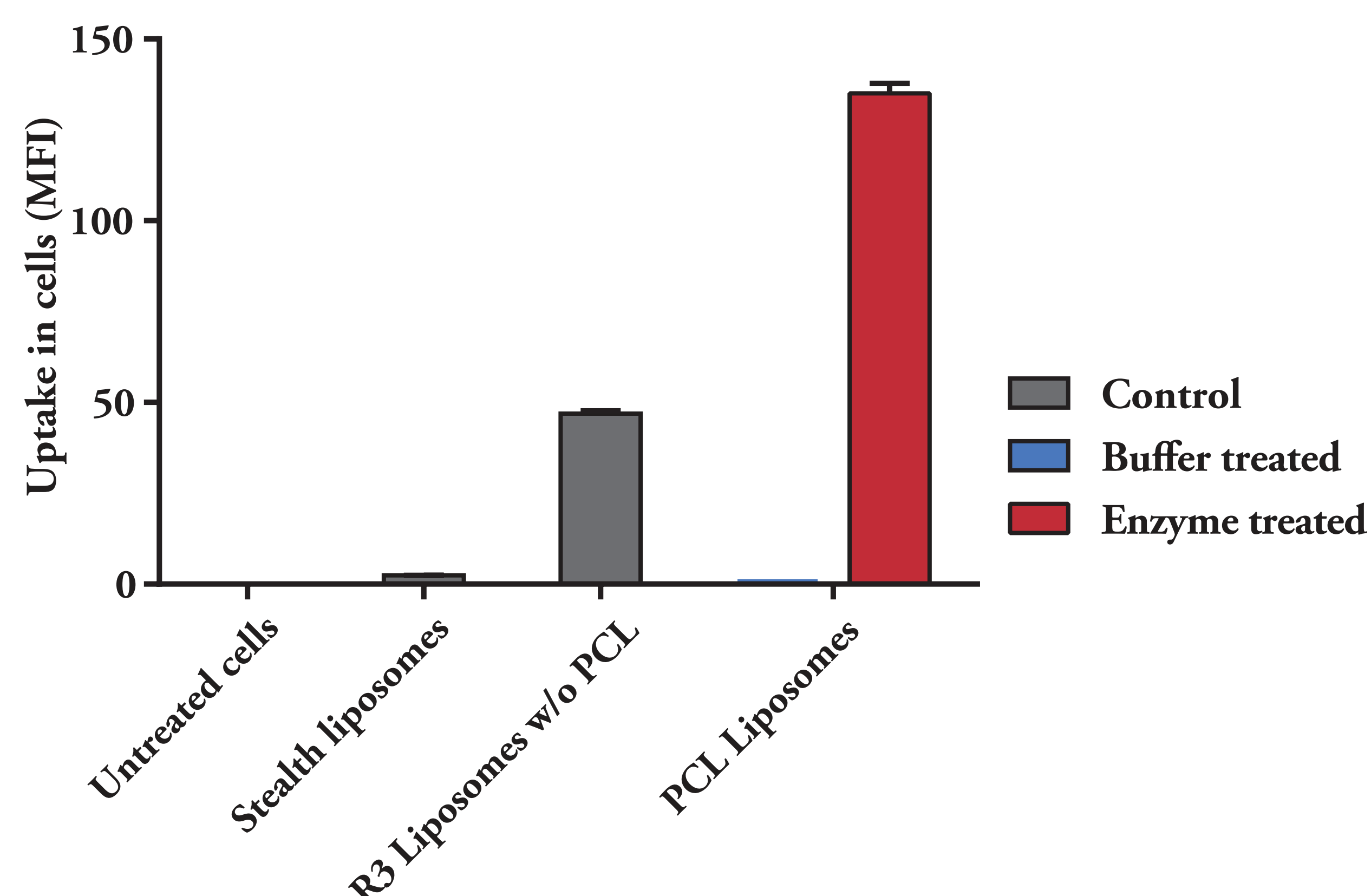


Enzymatic responsive charge-switch



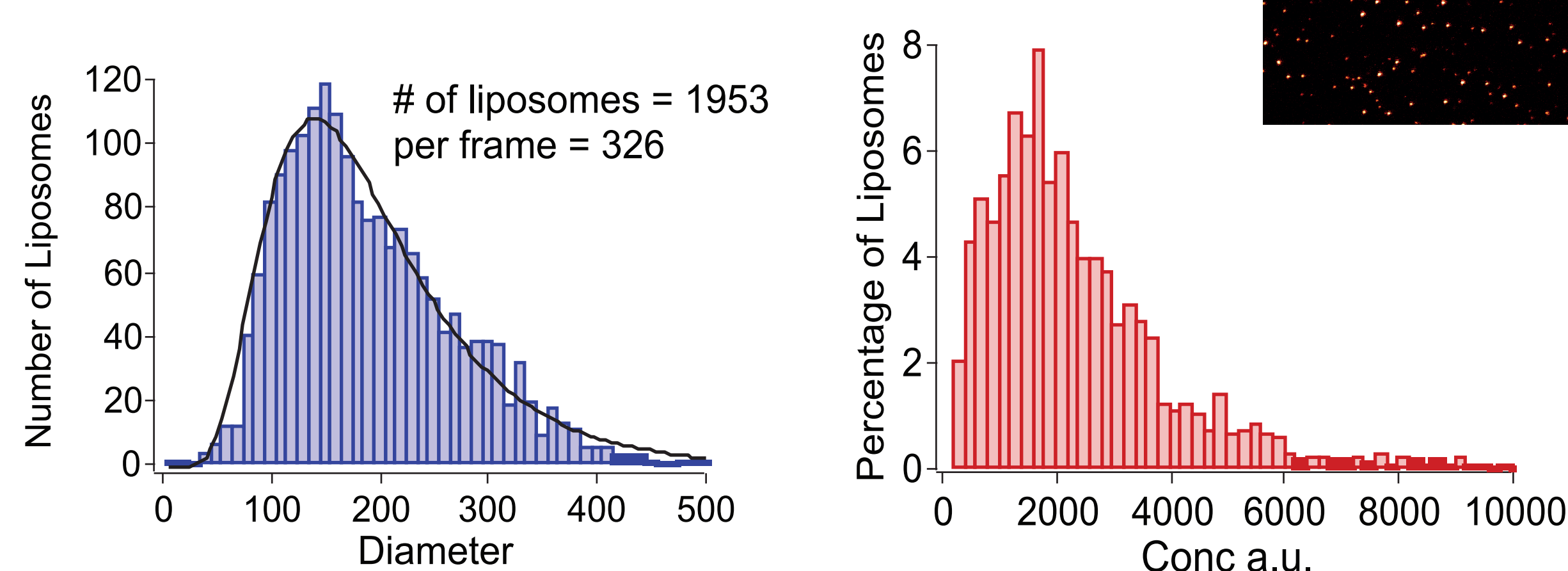
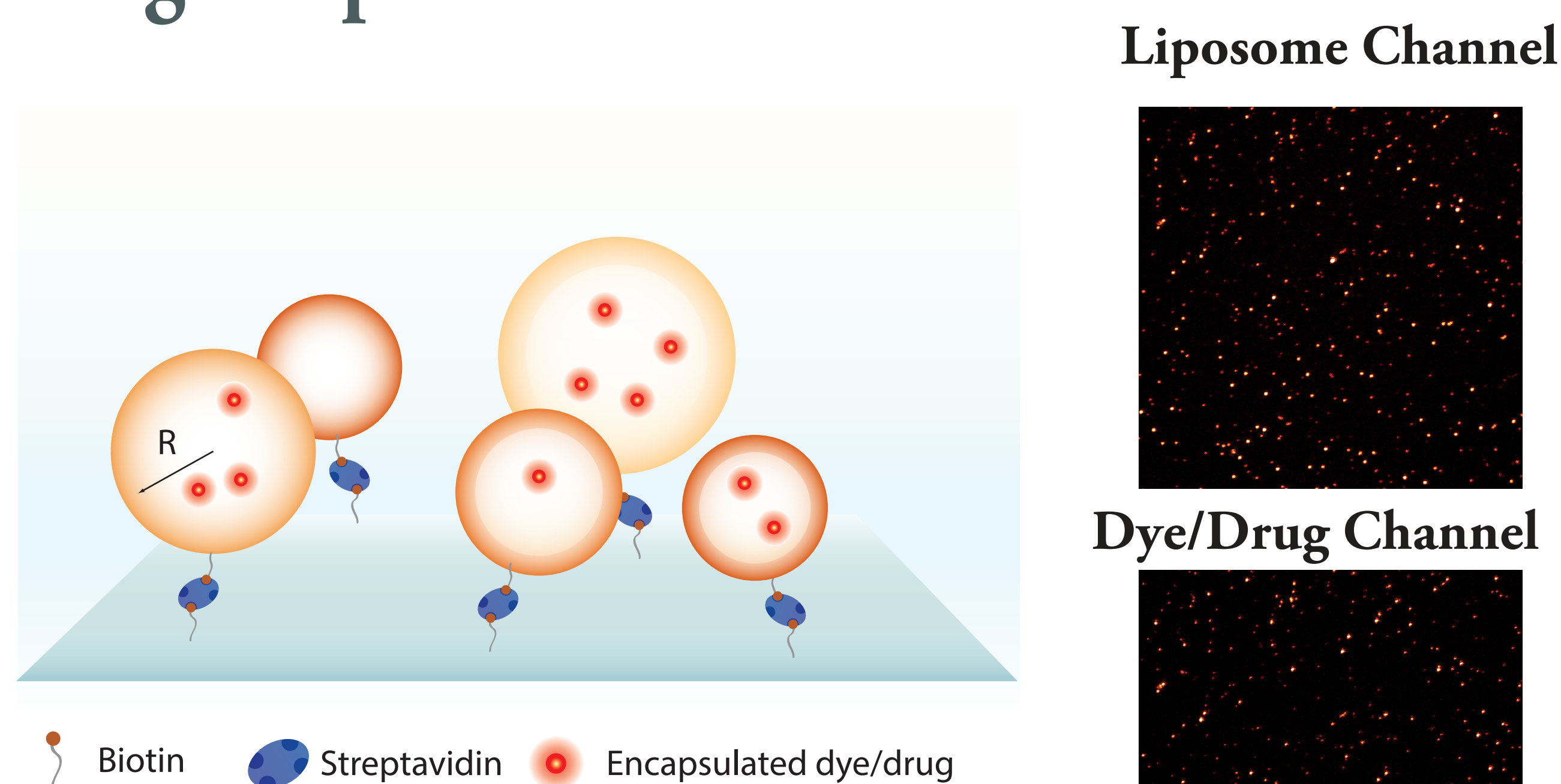
The MMP enzyme treatment shifts the liposomes surface charge from negative to positive due to removal of PEG and the four glutamic acid residues.

Enzymatic responsive uptake



The shift in surface charge facilitates interaction with the negatively charged cell membrane leading to increased uptake of MMP enzyme treated liposomes in HT1080 cells after 3 h incubation.

Single Liposome characterization



Single liposome assay for characterization of heterogeneities in the physio-chemical properties of individual liposomes. Here is presented preliminary results for size and drug concentration of single liposomes.

Conclusion and Perspectives

Incorporation of PCL makes the liposomes responsive to enzyme environment and provides them with a charge switch that controls their interaction with cells and thereby the drug delivery.

PCL is cleaved by MMP which is overexpressed in the brain under inflammatory conditions. The delivery system is thereby optimized for drug delivery following stroke and will be tested in stroke models. We are now implementing novel single liposome characterization assays to facilitate a deeper mechanistic understanding and provide new insights for optimizing the drug delivery system, potentially allowing us to create membrane fusiogenic liposomes.